TERA News

Notes from the March 1997 *ITER* Peer Review Meeting

ITER Peer Review Meeting Summary

March 6 and 7, 1997 University of Cincinnati, College of Medicine Cincinnati, Ohio USA

Assessments for dichloromethane (methylene chloride), cadmium and perchlorate were reviewed by a panel of risk assessment experts on March 6 and 7, 1997. This meeting was conducted by Toxicology Excellence for Risk Assessment (TERA), a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessments.

The peer review meeting began with a discussion of conflict of interest. Prior to the meeting each reviewer certified that he or she did not have a conflict (real or appearance) for each assessment and sponsor. Possible conflicts were discussed with the reviewer (and the TERA Board of Trustees, as needed) to determine if measures were needed to manage the conflict (or appearance). Options include excluding the reviewer from that chemical's discussion and consensus, or allowing the reviewer to participate in the discussion but not be polled for consensus. The peer review panel discussed and agreed upon how to manage any potential conflicts. This is documented in Attachment A.

Dichloromethane: Carcinogenicity Issues

Sponsor: Health Canada Presenters: Dr. Robert Liteplo and Ms. Bette Meek, Health Canada Chair: Dr. Michael Dourson, TERA

Review Panel:

- Dr. Robert Benson, U.S. EPA, Region VIII
- Dr. John Christopher, California EPA
- Dr. Gary Diamond, Syracuse Research Corporation
- Dr. Michael Dourson, Toxicology Excellence for Risk Assessment
- Dr. Marvin Friedman, Cytec Industries, Inc.
- Ms. Annie Jarabek,* U.S. EPA, National Center for Environmental Assessment
- Dr. George Leikauf,** University of Cincinnati
- Dr. Kenneth Poirier, The Procter and Gamble Company
- Dr. Jon Reid, University of Cincinnati
- Ms. Ruthann Rudel,* Silent Spring Institute

* Due to travel delays these two reviewers were not present for most of the dichloromethane discussion.

** Dr. Leikauf was asked in an ad hoc capacity to review this file as a specific area expert.

Presentation

Health Canada presented several issues related to the carcinogenicity of dichloromethane (DCM). These issues were taken from a submission made to Health Canada by the Halogenated Solvents Industry Alliance (HSIA). The submission consisted of data developed subsequent to Health Canada's 1993 assessment of dichloromethane under the Canadian Environmental Protection Act, and conclusions drawn by HSIA that these new data indicate that the 1993 assessment should be revised.

DCM is a widely used industrial chemical which has been found to result in an increased incidence of benign and malignant liver tumors in male and female mice, and benign (females only) and malignant (males and females) lung tumors in mice. In rats, DCM has been found to cause an increase in benign mammary tumors (male and female) and a borderline increase in malignant liver tumors in females. In Health Canada's 1993 assessment, DCM was classified as "probably carcinogenic to humans" (Group II) based on the weight-of-evidence in laboratory animals and evidence of mutagenicity and genotoxicity. The available epidemiological data were considered to be inadequate for the purposes of hazard identification for carcinogenicity in humans. In conducting a quantitative cancer risk assessment, Health Canada acknowledged significant species-differences in the metabolism of DCM which are believed to render the mouse more sensitive than rats or humans. Therefore, a PBPK model was used in calculating the Tumorigenic Dose-05s.

The most significant issue raised by HSIA was whether the tumors seen in the mouse following a cancer bioassay were an appropriate endpoint for determining whether DCM poses a carcinogenic risk to humans. Based on recently acquired data which they submitted to Health Canada in support of their position, HSIA claimed that the tumors seen in mice are both quantitatively and qualitatively irrelevant to an assessment of the carcinogenicity of DCM in humans. A secondary issue raised by HSIA was whether the results of the epidemiological studies are inconsistent with risk estimates derived from rodent bioassays.

The purpose of this peer review was not to review a particular assessment for DCM, but rather to review the statements made by HSIA in light of the data that they submitted to Health Canada and to answer the question: Based on preliminary review, is the submitted information adequate to serve as a basis for the contention that the mouse is an inappropriate model for the carcinogenicity of DCM in humans?

A total of eight papers relating to species differences and mechanisms of induction of tumors, and five papers relating to epidemiological studies of DCM were provided by Health Canada as being central to this review because these were the studies cited by HSIA in support of their position. Health Canada acknowledged that additional studies may be important, and that their literature search has not been updated. However, this was not considered necessary for the purposes of this preliminary review, which would constitute the basis, in part, for evaluation of the need to conduct a more complete review of all relevant data. That is, the reviewers were asked to provide comment on the issues highlighted by Health Canada (i.e., those in the HSIA submission) based solely on the data in the studies submitted by HSIA in support of their position.

In order to answer this question, Health Canada identified two main issues to be discussed. These issues were taken verbatim from the submission by HSIA, and Health Canada presented a written response to each of these issues. The peer review panel was then asked to review the data submitted by HSIA to support each issue and provide a consensus opinion as to whether these data did in fact provide sufficient evidence to support HSIA's position. The discussion was based around these issues.

ISSUE A: HSIA stated that, "Sophisticated studies of enzyme distribution in mouse, rat and human liver and lung tissue now provide strong biochemical support for the conclusion that the increases in lung and liver tumors seen in mice exposed in 2-year bioassays to high levels of methylene chloride are unique to that species..." The basis for this conclusion was described by HSIA in three parts, listed as Issues A.1 to A.3.

Issue A.1:

HSIA's position:

"The liver and lung tumors in mice are caused by a genotoxic mechanism involving metabolites of the glutathione pathway. The glutathione conjugate, a principal metabolite of this pathway, is reactive but highly unstable. Because of its instability, this conjugate must be generated in close proximity to DNA to produce a genotoxic effect. This can occur only where high enzyme activity, in particular that of GST5-5 (5-5 mRNA) is present in the nucleus of mammalian cells."

Health Canada's response:

It is generally agreed that metabolites of the glutathione pathway are likely to be responsible for the tumorigenic potency of DCM. Specifically, the tumorigenic metabolite is likely to be S-chloro-methylglutathione, the formation of which is catalyzed by glutathione S-transferase (GST). However, while this metabolite is indeed reactive, the data submitted by HSIA do not support the contention that it is so highly unstable as to require generation within the nucleus to be toxicologically relevant. Health Canada asserts that these data show that the reactive metabolites of DCM can, in fact, be generated outside of the cell and still result in genotoxic and mutagenic effects. In particular, the studies by Graves et al. (1994, 1995) show that metabolites generated by the addition of an exogenous mouse liver cytosolic fraction (S9) and glutathione to cultured Chinese hamster ovary (CHO) cells increased the DCM-induced formation of single-stranded DNA breaks. Furthermore, the study by Graves and Green (1996) showed that the incubation of CHO cells with DCM, mouse S9 and glutathione increased the frequency of gene mutations. Since the ultimate metabolite appears to be capable of crossing the cell membrane, it would appear likely that it is not so highly unstable as to be incapable of crossing the nuclear membrane.

Health Canada also pointed out that the identification of mRNA for the GST enzyme in the nucleus does not necessarily reflect the localization of the enzyme itself.

Peer Review comments and consensus opinion:

The peer reviewers unanimously agreed with Health Canada that the data do not support HSIA's claim that the glutathione conjugate of DCM must be produced within the nucleus to be able to elicit an effect. One peer reviewer emphasized that no information has been provided to document the instability of the metabolite. It is simply an assertion that the metabolite is sufficiently unstable so as to require generation in close proximity to DNA in order to be reactive, but there is no substantiation of this argument.

This discussion was carried over into the subject of lung cancer. While the Clara cells are purported to be the actual target cells for DCM-induced cancer, the data of Mainwaring et al. (1996) show GSTT1-1 (one of the theta subclasses of GST which is thought to be responsible for the metabolism of DCM to its ultimate carcinogenic metabolite) to be absent from the large bronchioles in humans, and only found in a few Clara cells and ciliated cells at the alveolar/bronchiolar junction. One peer reviewer suggested that

even if the Theta GSTases were completely absent in human Clara cells (which data have not shown), enzymatic activity in proximal epithelial cells could result in metabolism of DCM which could affect the cells next to it (for example, it was pointed out that formaldehyde, another metabolite of DCM, can cross cell membranes).

Issue A.2:

HSIA's position:

"Very high concentrations of transferase 5-5 mRNA have been identified in mouse liver and lung samples and are found to be localized in the nucleus. These enzymes, which are necessary to metablize methylene chloride by the glutathione pathway, account for the unique sensitivity of the mouse to the genotoxic effects of methylene chloride. In the absence of such enzyme activity, as is the case for human tissues, no mutagenic effect is detectable."

Health Canada's response:

The data have shown the presence of mRNA for the Theta subfamily of glutathione S-transferase (GSTT1-1) in the nucleus of mouse lung and liver cells, but the actual enzyme itself has not been quantified, and the methods used by Mainwaring et al. (1996) to detect the mRNA were at best, semi-quantitative. Therefore, the fact that no significant amounts of GSTT1-1 mRNA have not been found in the nuclei of human hepatocytes does not mean that there is no enzyme there. Furthermore, several investigators have, in fact, reported -- and quantified -- GSTase activity with DCM in human liver and lung cytosolic extracts (for example: Graves et al., 1995; Mainwaring et al., 1996) and mRNA for GSTT1 has been detected in sections of human liver and lung tissues (Mainwaring et al., 1996).

Peer Review comments and consensus opinion:

The peer reviewers agreed that based on the data submitted, one could not conclude that there was no enzyme activity in the nucleus of human tissues. Specifically, they reiterated Health Canada's position that the fact that the studies reported findings for mRNA for GSTT1-1 rather than for the enzyme itself, and that the methods were only semi-quantitative, meant that one could draw few conclusions. One peer reviewer also questioned the source of the human tissues. Because mRNA is so unstable, it is important to document tissue preparation, which was not done by Mainwaring et al. (1996).

It was also pointed out that while Mainwaring et al. (1996) did report the distribution of the GSTT2-2 enzyme in human, mouse and rat tissues, the antibody used by Mainwaring et al. (1996) in these assays was raised against recombinant rat Theta enzyme GSTT2-2, and the degree of cross-reactivity between rat antibodies and human tissues is not known. Health Canada also clarified that it is the GSTT1-1 enzyme which is responsible for metabolizing DCM to the ultimate carcinogen, and no measurements of this subclass of the GSTase were made in the human tissues. That is, GSTT1-1 measurements were specifically for levels of mRNA (using nucleotide probes), while GSTT2-2 measurements were for the enzyme (using the rat antibody), as well as for mRNA in the mouse and rat.

Finally, one peer reviewer called attention to the finding by Mainwaring et al. (1996) that the antibody probe did reveal high concentrations of GSTT2-2 in the bile ducts of human liver. Health Canada agreed that this may be of concern since one preliminary report of an epidemiological study (Lanes et al., 1993) indicated an increase in biliary cancer. It was clarified, though, that the enzyme found at high levels in the human bile duct was GSTT2-2, and it is the GSTT1-1 enzyme that is of greater concern (but could not be looked for directly because no antibody is available for GSTT1-1).

Issue A.3:

HSIA's position:

"High concentrations of transferase 5-5 mRNA were not identified in rat or human liver tissue. Similarly, transferase 5-5 mRNA was not concentrated in rat lung tissue and has not been detected in the human-- ... lung tissue analyzed to date."

Health Canada's response:

The data do support the conclusion that there are species-specific quantitative differences in the glutathione-mediated metabolism of DCM which are likely to be related to the higher susceptibility of the mouse. However, the data do show that human cells can, in fact, metabolize DCM by this pathway, albeit at a lower level than the mouse. For example, Mainwaring et al. (1996) report data on the ability of human lung and liver samples to metabolize DCM by GSTT1-1, one of two Theta-family glutathione transferases.

Health Canada provided a table listing studies in which levels of GSTase-dependent metabolism of DCM in vitro have been quantified. In addition to the forementioned studies by Mainwaring et al. (1996) and Graves et al. (1995), studies by Reitz et al. (1989; study not provided to reviewers) and Bogaards et al. (1993 study not provided to reviewers) were presented as evidence that GSTase activity has been measured and quantified in human lung and liver cytosols. The levels are clearly lower in the human tissues than in the mouse, but are detectable nonetheless. This supports the conclusion that while the mouse may be more sensitive than the human to the carcinogenicity of DCM, the findings in the mouse cannot be considered to be qualitatively irrelevant to humans.

Health Canada also states that the absence of mutagenic effects in human tissues, as referenced by HSIA, is not supported by the data. Specifically, HSIA based its statements on the absence of induction of DNA single strand (ssDNA) breaks by the alkaline elution assay. Health Canada contends that this assay is often insensitive, and furthermore that it is not clear what a lack of ssDNA breaks means with regard to genotoxicity.

Peer Review comments and consensus opinion:

With regard to the lack of ssDNA breaks in human cells, one peer reviewer called attention to the results of the studies by Graves et al. (1995) as illustrated in Figure 7 of that paper. This figure showed the results of alkaline elution assays as a measurement of ssDNA breaks in human hepatocytes exposed to either DCM or 1,2-dibromoethane. These were the only data presented that could support an argument about the lack of ssDNA breaks in human hepatocytes, but it was noted that the control curve of the assay using DCM was as steep as the high dose of the assay using 1,2-dibromoethane. Furthermore, the results were from a single experiment so that error bars could not be generated. Health Canada indicated that this assay would need to be replicated before any confidence could be placed in the results.

One of the peer reviewers asked Health Canada what would be considered acceptable evidence that DCM does not have genotoxic activity in human hepatocytes. It was emphasized that primary cultures of human hepatocytes are difficult to establish and use in assays. It was stated by another peer reviewer that it is more difficult to demonstrate the absence of something than it is to demonstrate the presence of something, but that the data presented were clearly not sufficient to demonstrate that DCM does not have genotoxic activity in human hepatocytes. Health Canada agreed with this conclusion.

ISSUE B

HSIA's position:

"We believe that the epidemiology studies.... which show no overall increased cancer risk in workers exposed to relatively high concentrations of methylene chloride, provide strong evidence in support of the conclusion that there are clear inter-species differences in carcinogenicity..... Indeed, the epidemiology results are inconsistent with risk estimates based on extrapolation from rodent bioassays."

Health Canada's response:

Health Canada has determined the epidemiological studies to be of insufficient sensitivity, especially for the organs of interest (e.g., liver), to be able to draw conclusions. During the presentation, Health Canada indicated that their position diverged slightly from that of the Occupational Safety and Heath Administration (OSHA), which published their Final Rule on Occupational Exposure to Methylene Chloride in January, 1997. In this Rule, OSHA stated that the epidemiological data are consistent with the laboratory animal data and are 'suggestive' of carcinogenicity. Health Canada has taken the position that the data are too inconsistent and that conclusions cannot be drawn from the human studies.

Peer Review comments and consensus opinion:

The peer reviewers agreed with Health Canada's conclusions on the weight-of-evidence for the human studies. Some wording changes were suggested:

* One peer reviewer suggested a wording change with regard to the overall conclusion of the epidemiological database to indicate that the epidemiological data are not inconsistent with the animal data. Health Canada agreed with this suggestion.

* In Health Canada's description of the study by Lanes et al. (1993), it is concluded that a causal association between biliary cancer and DCM exposure is 'plausible.' However, Health Canada acknowledged that the biliary cancer reported in this study was too statistically unstable to be regarded as a true effect. One peer reviewer pointed out that you can't have an effect if you don't have a cause. Health Canada agreed to change the wording in this section accordingly.

* One of the peer reviewers suggested that the study by Gibbs et al. (1996) is perhaps a stronger study than is indicated by Health Canada's description, and consideration should be given to a slight wording change.

As an aside, one peer reviewer asked whether Health Canada was aware of the liver toxicity data in humans (morbidity studies) and offered to make these available to Health Canada. There was also some discussion among the peer reviewers about the value of looking at biliary cancer across human cohorts (because it is such a rare tumor). Health Canada may consider doing this, but it was of questionable value according to the discussion and not likely to shed additional light on the question of human cancer.

Overall Panel Recommendations:

* The panel agreed that Health Canada had responded well to the issues raised by HSIA. In conclusion, they agreed that the data submitted by HSIA do not support the conclusion that the tumorigenic findings in the mouse are irrelevant to humans, and furthermore, that the human data have not been shown to be

inconsistent with the risk estimates derived from rodent models.

* It was recommended that Health Canada provide a more critical review of the study by Graves et al. (1995), in particular the data shown in Figure 7 (ssDNA breaks induced in human hepatocytes by DCM or 1,2-dibromoethane).

* Minor wording changes were suggested by peer reviewers to improve the text describing the human weight-of-evidence (see Issue B above).

* One peer reviewer suggested that Health Canada consider mentioning recent data generated by CIIT in their response to HSIA. These data were not explicitly considered at the peer review meeting, but it was felt that they were of sufficient importance for Health Canada to consider including.

References

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Mainwaring, G.W., S. Williams, J.R. Foster, J. Tugwood and T. Green. 1996. The distribution of Theta-class glutathione S-transferases in the liver and lung of mouse, rat and human. Biochem. J. 318 (part 1): 297-303.

Reitz, R.H., A.L. Mendrala and F.P. Guengerich. 1989. In Vitro metabolism of methylene chloride in human and animal tissues: Use in physiologically based pharmacokinetic models. Toxicol. Appl. Pharmacol. 97: 230-246.

Cadmium Inhalation Reference Concentration (RfC)

Sponsor: U.S. Environmental Protection Agency (EPA), Region VIII

Presenter: Dr. Robert Benson, EPA

Chair: Dr. Michael Dourson, TERA

Review Panel:

Dr. John Christopher, California EPA

Dr. Gary Diamond, Syracuse Research Corporation

Dr. Michael Dourson, Toxicology Excellence for Risk Assessment

Dr. Marvin Friedman, Cytec Industries, Inc.

Ms. Annie Jarabek,* U.S. EPA, National Center for Environmental Assessment

Ms. Bette Meek, Health Canada

Dr. Kenneth Poirier, The Procter and Gamble Company

Dr. Jon Reid, University of Cincinnati

Ms. Ruthann Rudel, Silent Spring Institute

* Ms. Jarabek was not polled for consensus - see Attachment A for details.

Presentation

Region VIII of the U.S. EPA presented an RfC for cadmium. It was clarified that the RfC was specifically for cadmium oxide and salts of similar or greater solubility. Uptake in the respiratory tract is highly dependent on the chemical form since that determines in vivo solubility. Many studies have been conducted in humans exposed occupationally to cadmium by the route of inhalation. Renal tubular dysfunction was proposed as the effect of concern in cadmium-exposed individuals, with increased excretion of beta 2-microglobulin in the urine being diagnostic for this type of kidney damage. Because human data are available, the presentation and the assessment itself focused on the human studies, with data from laboratory animals being used to supplement areas in which the human data are weak.

The key human studies have been summarized by Thun et al. (1991). Most of the studies used excretion of beta 2-microglobulin in the urine as a marker for kidney toxicity, but several different definitions were used to determine at what level it was considered to be adverse. One study used excretion of retinol binding protein. It was noted that overall there is a good agreement among the occupational studies with respect to the relationship between exposure and urinary excretion of beta 2-microglobulin.

The proposed RfC was based on a cross-sectional study by Jarup et al. (1988) of humans occupationally exposed to cadmium oxide dust in a Swedish battery factory. This study was chosen over the other human studies because it had the largest cohort and the data were presented in a manner suitable for risk assessment purposes. All workers who were employed for at least three months between 1931 and 1982 were included in the cohort if at least one measurement of urinary beta 2-microglobulin had been made. Kidney function of the exposed workers was determined by a radioimmunological assay of beta 2-microglobulin in urine. The authors defined an effect level as urinary beta 2-microglobulin exceeding 35 ug beta 2-microglobulin /mmole creatinine (309 ug beta 2-microglobulin /g creatinine). This level of excretion represented the 97.5 percentile of the distribution of beta 2-microglobulin excretion in the general population.

The workers were assigned to one of six exposure groups, with exposure being expressed as the mean cumulative cadmium exposure in units of ug-years/cu.m. A strong dose-response relationship was apparent. Using regression analysis, a response rate for renal tubular proteinuria of 5% (chosen as the upper limit of the NOAEL) was found to correspond to a cumulative exposure of approximately 590 ug-years/cu.m. Adjusting this value to a continuous exposure scenario (see section on Dose-Response) yielded a NOAEL of 3 ug/cu.m. An uncertainty factor of 10 was proposed to protect sensitive individuals, so that the proposed RfC is 0.3 ug/cu.m or 3E-4 mg/cu.m.

Hazard Identification

The presentation focused on the kidney as the target organ for the toxic effects of cadmium. While renal toxicity has long been known to result from exposure to cadmium, one of the peer reviewers questioned whether sufficient consideration had been given to the respiratory tract. In general, it appeared that the available data on respiratory tract effects in humans indicates that these occur at exposure levels higher than those associated with renal toxicity, but it was pointed out by a reviewer that this may be due to the fact that the only measures of respiratory tract effect were rather insensitive (e.g., spirometry) in comparison to measures assessing renal effects.

Respiratory tract effects measured by various lung function tests were indicated in both the Lauwerys et al. (1979) and Smith et al. (1976) studies. In addition, a study by Davison et al. (1988) suggested pulmonary effects at exposure levels lower than those associated with renal toxicity, although the clinical significance of these effects was not clear. Underlying mechanisms of the effect on pulmonary function have not been investigated. A reviewer also pointed out that respiratory tract effects were seen in a rat subchronic inhalation study by Kutzman et al. (1986). When these respiratory tract effects are dosimetrically adjusted for interspecies differences, the resultant human equivalent concentration falls in the range of 50 ug/cu. m, which is within the same magnitude as the renal effects. Recent preliminary toxicokinetic modeling efforts (Foureman et al., 1996) indicate that the air exposure for lung function effects (6.5 ug/cu. m) is even closer to that causing renal effects (1.4 ug/cu. m), which raised concern for respiratory tract effects as co-critical when the differences in sensitivity of the effect measures was considered. Other modeling efforts have indicated that respiratory tract cancer risk of inhaled cadmium is also greater by inhalation than the oral route (Oberdsrster, 1990).

The peer reviewers asked about the results of the NTP bioassay, which were not described in the assessment done by Region VIII. Dr. Benson presented overheads summarizing the findings of the NTP bioassay. Effects were noted in the respiratory tract at all exposure concentrations and a trend with dose appeared discernable, but it was not known how these concentrations would relate to the exposures in the human studies. Dr. Benson agreed that the lung function tests in people do not provide a very sensitive measure of potential adverse effects in the respiratory tract. Dr. Benson further agreed to conduct a more extensive analysis of the NTP bioassay and to make the dosimetric adjustments to determine whether the respiratory tract lesions might be a co-critical effect.

Some questions were raised by the peer review panel about the database for reproductive and developmental endpoints. The panel made note of studies by Baranski et al. (1984, 1986) in which neurobehavioral effects had been reported in rats exposed in utero. The toxicological significance of these effects had been questioned by Dr. Benson, but the panel felt that the human equivalent concentrations should be calculated to put these endpoints into better perspective with the lesions in the kidney and respiratory tract. In addition, one peer reviewer requested greater discussion of the levels at which neurological effects are observed in occupationally exposed populations in an attempt to ascertain, if developing fetuses are more sensitive (as is the case in animal studies), whether this might be a co-critical

effect. Other reviewers maintained, however, that the observation of neurological effects in exposed adults cannot be used to draw conclusions about possible effects in fetuses.

Finally, one of the peer reviewers asked that some consideration be given to bone as another possible target organ. Recently published studies in rats and dogs have indicated that effects in the bone may not be secondary to renal toxicity, as had been previously thought. Additional studies were provided to Dr. Benson for his consideration and incorporation into the file as appropriate.

In summary, the peer review panel agreed that the study by Jarup et al. (1988) was appropriate to serve as the critical study based on the findings of renal toxicity in an occupationally exposed cohort, but that explicit consideration should be given to the respiratory tract as a possible co-critical target. Additionally, bone and reproductive/developmental effects should be looked at more closely. Other human studies were also discussed, and it was suggested that all of the human and animal studies (including neurobehavioural, reproductive and developmental, and bone effects) should be presented in the format of a summary table with a discussion of the strengths and weaknesses and possible confounding factors (such as lack of data on smoking) for each study. This table should include both internal dose metrics (blood and urine cadmium concentrations where available) and calculated human equivalent air concentrations for all of the non portal-of-entry endpoints, so that the appropriate critical effect can be determined with greater confidence. Overall, it was concluded that the Jarup et al. (1988) study was the best single study to use for quantitative analysis of renal effects, particularly because it was a larger study than the others.

Dose-Response Assessment

Dr. Benson indicated that he had done a benchmark dose analysis of the data in Jarup et al. (1988), using a quantal model both with and without a threshold term and based upon extra risk, but there was not a good fit to the data. Therefore, he used the regression analysis reported in the Jarup paper to determine the exposure-response relationship. The NOAEL was defined as the 5% prevalence of beta 2-microglobulin, which was found to correspond to a cumulative exposure of 590 ug-years/cu.m.

In order the convert the occupational exposure to a continuous exposure, Dr. Benson multiplied the NOAEL of 590 ug-years/cu.m. by several factors:

* 10 cu.m per day / 20 cu.m per day to extrapolate from an occupational ventilation rate to a ventilation rate for the general population;

* 5 days / 7 days to extrapolate from a 5-day work week ;

* 1 / 70 years to account for exposure over a lifetime.

The resulting NOAEL was 3 ug/cu.m (equivalent to 3E-3 mg/cu.m).

The NOAEL was divided by a total uncertainty factor of 10 to derive a proposed RfC of 3E-4 mg/cu.m.

In establishing the NOAEL for this study, Dr. Benson accepted the authors designation of adverse effect as being anything above the 97.5 percentile in urinary excretion of beta 2-microglobulin (which was 35 ug beta 2-microglobulin /mmol creatinine). The panel discussed the selection of this cut-off. It was noted that there was no way to account for whether an individual was just slightly above this cut-off or 100-fold above it; they were both simply listed as 'responders.' Dr. Benson showed data from another study in occupationally exposed workers (Falck et al., 1983) which showed that responders tended to have much

higher levels of urinary beta 2-microglobulin and that few individuals would actually be around the cut-off level.

The reviewers also questioned whether it was best to use atmospheric concentrations of Cd in the dose-response analysis rather than a dosimeter such as blood or urinary levels of cadmium, from which one could then determine a corresponding atmospheric concentration. Dr. Benson indicated that these are all comparable endpoints, but that it is easier to deal with atmospheric concentrations. It was requested, nonetheless, that internal dose metrics be given for any effects other than those at the portal-of-entry because the potential exposure misclassification resulting from the use of exposure estimates rather than internal measures may weaken the observed association between exposure and effect. At the least, it was requested that the assessment show NOAELs calculated using both exposure levels and internal dose metrics. One of the peer reviewers requested that additional information be sought on how dose reconstruction had been done in the Jarup et al. (1988) study.

One reviewer questioned the method used to extrapolate from the NOAEL of 590 ug-year/cu.m to determine an equivalent concentration for continuous exposure over a lifetime. In particular, it was questioned whether it was appropriate to divide the NOAEL by 70 years. It was clarified that the level of 590 ug-years/cu.m was a cumulative exposure and that this was divided by 70 years to determine a level that would be comparable for a lifetime of exposure. The reviewer requested that Dr. Benson attempt to get data to determine the actual exposure concentrations and number of years each worker was exposed, rather than use Haber's "Conjecture" to justify a divisor of 70 years. It could then be determined whether dose rate or cumulative dose is a more appropriate measure of exposure. It was acknowledged by the reviewer that cumulative dose may be more important in eliciting renal toxicity, but that dose rate could a be more important determinant for respiratory tract and bone effects. The peer reviewers also questioned whether the factors of 10 cu.m per day / 20 cu.m per day to extrapolate from an occupational ventilation rate to a ventilation rate for the general population; and 5 days / 7 days to extrapolate from a 5-day work week were appropriate. No resolution was reached on this issue since it was again expressed that Dr. Benson should try to obtain actual exposure data.

Uncertainty Factors: An uncertainty factor (UF) of 10 was proposed to protect sensitive individuals. The panel agreed with this choice.

Subchronic to Chronic: This area of uncertainty was accounted in the assessment by dividing the exposure over a lifetime. If the NOAEL is expressed for chronic exposure, then an UF for this area is not needed. This was an unresolved area, however, since the extrapolation method was questioned by the peer reviewers. The Adamsson (1979) paper should be consulted to see if it helps resolve the issue.

Database: It was suggested that additional information about the exposure levels at which neurobehavioral effects were reported might help justify the choice of an UF of one for this area (assuming that the human equivalent concentrations were higher than those associated with kidney effects).

Confidence in the Value

Dr. Benson expressed a high degree of confidence in the critical effect of renal tubular dysfunction. He acknowledged that some questions remain about the reproductive and developmental endpoints, but indicated that an additional UF was not warranted on this basis. He expressed medium confidence in both the database and the RfC. The peer reviewers stated that it was difficult to know how much confidence to have until some of the outstanding issues have been resolved, particularly whether or not the respiratory tract is co-critical target organ with the kidney.

Recommendations and Outstanding Issues

The reviewers had a number of suggestions for further work and requests for additional information; however, the next steps for review of the cadmium RfC were not explicitly discussed at the meeting. Reviewers were polled after the meeting and generally agreed that because the issues identified for the cadmium RfC were generally to seek and present further information and confirm the appropriate critical effect, that the revised package can be reviewed by mail and teleconference. However, if significant new issues arise, a meeting review may be necessary. There was some discussion on reviewing both oral and inhalation non-cancer values together so as to make better use of the database and help to elucidate the relationship between exposure levels associated with respiratory tract versus renal effects.

* Add a summary table of the findings of all of the human studies similar to that presented in Thun et al. (1991). Provide more information about the strengths and weaknesses of each study and possible confounders (such as lack of information about smoking).

* Include a write-up of the more recent study by Jarup (1994) including a discussion of the shortcomings of this study [e.g., the data on beta-2 microglobulin excretion are for aged workers (> 60 years) and no correction was made for the normal increase in beta-2 microglobulin excretion as a function of age]. Include description of Kutzman et al. (1986) and NTP (1995) with human equivalent concentrations.

* Make sure that it is clear that this RfC is for cadmium oxide; perhaps add a statement indicating the importance of chemical speciation on uptake.

* Briefly describe the difficulty in assessing possible respiratory tract effects in Smith et al. (1976) and Lauwerys et al. (1979), which results from the relative insensitivity of the methods (basic spirometry) used in these studies.

* Calculate human equivalent concentrations for the NTP bioassay in rats and mice to determine how the exposure levels in this study compare with the human exposure levels. This will help answer the question of whether effects in the respiratory tract might be co-critical with the renal effects.

* If appropriate, incorporate new references on studies in rats and dogs which suggest that effects seen in the bone may not be secondary to the kidney effects as has been previously thought.

* If available, obtain more information on the actual exposure levels in Jarup et al. (1988) to replace or modify the default assumptions used to calculate the human equivalent concentrations from the cumulative exposure data that were provided by the authors. It was acknowledged, however, that these data may not be easily obtained as the reference was a Swedish thesis report published in 1983 (reference #10 in Jarup et al., 1988).

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Perchlorate Oral Reference Dose (RfD)

Sponsor: Perchlorate Study Group

Presenter: Ms. Joan Dollarhide and Dr. Michael Dourson, TERA

Chair: Dr. Kenneth Poirier, Procter and Gamble Company

Review Panel:

Dr. Robert Benson, U.S. EPA, Region VIII

Dr. John Christopher*, California EPA

Dr. Gary Diamond, Syracuse Research Corporation

Dr. Marvin Friedman, Cytec Industries, Inc.

Ms. Annie Jarabek, U.S. EPA, National Center for Environmental Assessment

Ms. Bette Meek, Health Canada

Dr. Kenneth Poirier, Procter and Gambie Company

Dr. Jon Reid, University of Cincinnati

Ms. Ruthann Rudel, Silent Spring Institute

* Dr. Christopher was not polled for consensus - see Attachment A for details.

The sponsoring organization, the Perchlorate Study Group, arranged for two thyroid experts: Dr. James Fagin, University of Cincinnati Department of Endocrinology; and Dr. Charles Capen, Ohio State University Department of Veterinary Biosciences, to be present to answer questions from the panel.

One observer registered to make comments at the meeting. Dr. Daniel Caldwell, principal investigator of the Caldwell et al. (1996) study, provided comments and was available to answer questions from the review panel. In addition, TERA received written comments from Dr. Terry Harvey of the U.S. EPA's National Center for Environmental Assessment, which the chair summarized during the discussion portion of the meeting.

Presentation

Ammonium perchlorate has been widely used as a solid rocket propellant which has resulted in soil and water contamination at a number of sites in the U.S. Potassium perchlorate has been used therapeutically to treat hyperthyroidism resulting from Graves' disease. *TERA* evaluated the toxicity of perchlorates in order to develop a reference dose. The Perchlorate Study Group, a consortium of companies that use and/or manufacture perchlorates, sponsored the evaluation by *TERA* and the peer review.

Perchlorate has been studied primarily in human patients with Graves' disease. Graves' disease is an autoimmune disorder in which patients have antibodies to the TSH receptors in the thyroid. As a result, patients are hyperthyroid with thyroids that are actively pumping iodide and producing elevated levels of the thyroid hormones T3 and T4. Perchlorate acts to block iodide uptake thereby returning thyroid hormone levels to normal and controlling the symptoms of hyperthyroidism. Studies of perchlorate in Graves' patients range in duration from a single dose (Stanbury and Wyngaarden, 1952) to several weeks (Godley and Stanbury, 1954; Crooks and Wayne, 1960, Morgans and Trotter, 1960; Hobson, 1961; Johnson and Moore, 1961; Fawcett and Clark, 1961; Krevans et al, 1962; Gjemdal, 1963; Barzilai and Sheinfeld, 1966). Only one case study reports long-term treatment with perchlorate in one patient (22 years, Connell, 1981). Doses of perchlorate range from <1 mg/kg-day (Stanbury and Wyngaarden, 1952) to>20 mg/kg-day (Crooks and Wayne, 1960) with typical exposures in the range of 6-14 mg/kg-day. Effects observed include block of iodide uptake and iodide discharge by thyroid (Stanbury and

Wyngaarden, 1952), gastrointestinal irritation, skin rash (Godley and Stanbury, 1954; Crooks and Wayne, 1960) and hematological effects including agranulocytosis and lymphadenopathy (Crooks and Wayne, 1960; Morgans and Trotter, 1960). Seven cases of fatal aplastic anemia were reported at the same dose level (6-14 mg/kg-day) at which other side effects were observed (Hobson, 1961; Johnson and Moore, 1961; Fawcett and Clark, 1961; Krevans et al, 1962; Gjemdal, 1963; Barzilai and Sheinfeld, 1966).

Only two studies examined the effects of perchlorate in healthy volunteers. Burgi et al. (1974) studied perchlorate at 9.7 mg/kg-day on five subjects for eight days and Brabant et al. (1994) studied perchlorate at 12 mg/kg-day on five subjects for 4 weeks. Both studies observed effects on the thyroid at these doses.

Studies in laboratory animals range in duration from 4 days (Mannisto et al., 1979) to 2 years (Kessler and Krunkemper, 1966). None of the studies examined any organs other than the thyroid and all of the longer-term studies used doses that were too high to define a NOAEL. Of the short-term studies, Mannisto et al. (1979) defined a NOAEL at 1.5 mg/kg-day based on increased TSH levels and Caldwell et al. (1996), a 14-day drinking water study in rats, identified a NOAEL in males and a LOAEL in females of 0.1 mg/kg-day based on increased relative thyroid weight and TSH, and decreased T3 and T4 levels.

TERA proposed an RfD based on the Stanbury and Wyngaarden (1952) study because it identified the lowest LOAEL, was performed on humans, and was the more sensitive of the two most appropriate human studies. A definitive LOAEL of 1.4 mg/kg/day was chosen for acute disturbance of iodide accumulation in the thyroid. An overall uncertainty factor of 100 was recommended. A factor of 3 was applied with use of a minimal LOAEL; a factor of 3 with the use of a subchronic study because the endpoint is the beginning of a cascade of effects; and a factor of 3 for inadequacies of the database, particularly lack of chronic studies in rodents, limited developmental information, and no multi-generation study.

Hazard Identification

The database consists of information on patients treated with potassium perchlorate for Graves' disease, a few studies of short-term exposure in normal humans, and laboratory animal studies at high doses (which did not examine target organs other than the thyroid). Perchlorate competitively inhibites iodide transport into the thyroid.

The reviewers requested more clarification on the forms of perchlorate and additional information on dissociation constants or similar salts. Ms. Dollarhide stated that potassium perchlorate has been studied in humans and ammonium perchlorate is the compound of concern. Because the perchlorate salts dissociate completely when dissolved in water or aqueous tissues, exposure is to the ion, not a particular salt. Therefore, the RfD has been developed for the ion.

The panel concluded that the data were not sufficient to rule out effects of perchlorate on other organs, so it could not be determined that effects on the thyroid were the critical effect. In particular, the panel was concerned that developmental toxicity (i.e. impaired neurological development) could be a critical effect of perchlorate that has not been adequately examined in studies to date. In addition, a longer-term study in laboratory animals which examines multiple endpoints is needed. Prenatal and infant exposure was discussed. Hypothyroidism or iodine deficiency postnatally results in cretinism; however, studies of prenatal exposure and particularly, neurological endpoints would be helpful. Dr. Fagin stated that TR alpha- and beta-receptors appear at key developmental stages in the brain, suggesting they have a function. The panel also suggested that data on iodine deficiency, dietary goitrogens, and structurally similar ions be reviewed to determine if any useful dose-response information can be added to the

database.

The reviewers agreed that the available human data well define the mechanisms by which perchlorate acts on the thyroid, but that they provide little information on the dose-response relationship, or the likely effects in normal humans. Severe hematological side effects were seen in some Graves' patients treated with potassium perchlorate, leading to the discontinuation of its use. However, Dr. Fagin explained that perchlorate is now routinely used in several European countries to prevent side-effects from a cardiovascular drug, amioderone. Patients are treated with doses of less than 1 gram/day which does not result in the hematological effects observed earlier with doses greater than 1 gram/day. Dr. Fagin indicated that conventional wisdom is that the Graves' patients who had hematological effects were treated with greater than 1 g/day and perhaps there was contamination of the drug. The panel suggested that data on the current pharmaceutical use of perchlorate be reviewed, if possible, because if the hematological effects can conclusively be ruled out, then some of the existing studies [i.e. Burgi et al. (1974) and Godley and Stanbury (1954)] conducted at higher dose levels might provide additional information regarding dose-response in humans.

Although, in general, human studies are preferred over laboratory animal studies in developing an RfD, the reviewers concluded that lack of dose-response data precluded use of the human studies in this case. The reviewers were not comfortable with the use of Stanbury and Wyngaarden (1952) as critical, although if the hematological side effects are not a concern, some of the human studies can be reexamined to see if they provide more information on dose-response. The reviewers wanted to see all of the available data used to characterize and inform on dose-response in humans, and consider that a laboratory animal study might be more appropriate.

Assuming that the thyroid effects are critical, the reviewers concluded that the Caldwell et al. (1996) study may be a better critical study because it was conducted in the most appropriate route of exposure (drinking water), and established an adequate dose-response relationship. It was suggested that *TERA* consult with Dr. Capen to determine the biological significance of hormone level changes observed. In addition, Dr. Capen suggested that rats are more sensitive to perchlorate than humans because the rat thyroid is actively pumping iodide and therefore is more sensitive to the iodide blocking effect of perchlorate. The panel suggested that *TERA* consult with Dr. Capen to determine how to take this into consideration.

Dose-Response Assessment

Choice of Dose: The panel spent a large part of the discussion on what was the best measurement of thyroid effects for determining a NOAEL or LOAEL. For example, it was determined that while the measurement of iodide blocking and discharge from the thyroid may be the most sensitive indicators of perchlorate's effect on the thyroid, these endpoints might not be the best indicators of how perchlorate exposure may result in functional changes to thyroid metabolism. Although it was suggested that changes in hormone levels (TSH, T4 and T3) were a more appropriate measure of thyroid effects, there was much discussion of the significance of thyroid hormone changes and what degree of change in hormone blood levels could be considered biologically significant, rather than merely adaptive.

The Chair summarized the written comments from EPA as follows:

1. The only new data are from the Caldwell study of ammonium perchlorate, a 14-day study that did not identify a NOAEL, nor does it reflect lifetime risks.

2. The letter expressed concern that there are no metabolism or pharmacokinetic data on either

ammonium or potassium perchlorate which might reduce uncertainties related to the differences between the salts or related to extrapolation from animals to humans.

3. Uncertainties related to gender differences or children as sensitive subpopulations were not addressed.

The Caldwell et al.(1996) study was discussed at length. Dr. Caldwell, an observer, questioned the interpretation of 0.12 mg/kg/day as a LOAEL in Caldwell et al. (1996); rather, he thought it a NOAEL. He also indicated that the document attachment to that study includes some incorrect information and should be discarded. Ms. Dollarhide replied that *TERA* interpreted the effects seen at this dose as a LOAEL. The reviewers discussed which doses in this study showed statistically and biologically significant effects levels. Dr. Fagin indicated that the effects on T3 may be significant and may be due to effects on serum dehydrogenase activity. Dr. Caldwell explained that in his study design, he defined biological significance for all parameters as any change which was 2 standard deviations away from the mean in control animals. This was used rather than the normal range for rats. He had also predetermined that a LOAEL would be that dose level which caused both an increase in TSH and a decrease in T3/T4. Dr. Capen pointed out that the normal range for thyroid hormone levels in rats can be quite wide, and also depends on the laboratory which is doing the analysis.

The reviewers examined Table 3 of Caldwell et al. (1996) to determine what would be a NOAEL and LOAEL. Dr. Caldwell stated that he believed that the 0.44 mg/kg-day dose in males and the 0.12 mg/kg-day dose in females, were identified as NOAELs because only TSH levels and not T3/T4 levels were increased. One reviewer pointed out that the dose-response relationship begins at the lowest dose and the effects were seen whether they are statistically significant, or not. Dr. Capen pointed out the TSH levels in rats are 100 times higher than humans, with stronger thyroid stimulation in the rats than humans. The reviewers indicated that this would have to be factored in if Caldwell et al. (1996) were used.

One reviewer questioned what constitutes an adverse effect in the thyroid system; are all changes in TSH adverse? Ms. Dollarhide responded that they chose iodide blocking and discharge from the thyroid as the adverse effect as a conservative assumption, given no long term data. If the RfD was below a dose which caused complete blocking of iodide uptake, then other changes in thyroid function, such as changes in TSH levels should be prevented. One reviewer specifically asked Dr. Capen what percentage of increased TSH levels would be considered adverse. He replied that a 20% increase in TSH in rats would be considered adverse. Thus, one reviewer suggested that a 10% in TSH levels might be considered a NOAEL, or at least an appropriate level of response to use in benchmark dose modeling. Dr. Capen indicated that the rat is extremely sensitive to changes in TSH; and much more sensitive than humans to long-term stimulation. A modest increase in TSH (e.g. 20%) would lead to development of thyroid nodules (both benign and malignant) and he would predict one would see benign tumors. Reviewers discussed that thyroid follicular cell carcinogenesis would have to be considered.

Reviewers had questions about the dosing regimen in humans, the effect of dosing on determining an adverse effect, and what information was available regarding the half life of perchlorate. The difficulty in comparing the laboratory animal and human dosing was also acknowledged. Ms. Dollarhide replied that in most of the human studies, patients were dosed with 200-400 mg perchlorate 3 times per day. In addition, there was only 1 study which evaluated perchlorate metabolism and it estimated a half life for perchlorate of 20 hours. Dr. Fagin agreed that dose regimen might affect the response and stated that one would see the most dramatic changes early and then the system equilibrates, but it could lead to tumors. Dr. Caldwell suggested looking at a paper by Wilson which found that continuous exposure will result in equilibration. Dr. Fagin agreed that the system equilibrates at a new hormone level, the T3 and T4 will go back to normal , but TSH will not go back to normal. In human patients with elevated TSH, this would result in subclinical hypothyroidism. Dr. Capen said that long term stimulation is more likely to form

benign tumors and that human patients with iodine deficiency have huge thyroids. In addition, the likelihood of increased thyroid cancer incidence is much less for humans than for rats. Therefore, Dr. Caldwell concluded that using the increase in TSH as an adverse effect would be protective of any effects on T4. Dr. Capen said if perchlorate exposure were to decrease then hypertrophy and hyperplasia would return to normal.

The reviewers did not identify the critical effect level, but deferred this until a revised assessment with additional data could be considered. However, when asked about the assessment as proposed, the reviewers offered a number of comments. On the appropriate critical dose from the Stanbury and Wyngaarden (1952) study, they questioned whether the 1.4 mg/kg-day was the LOAEL and one reviewer indicated that the lowest dose (of 0.04 mg/kg-day) would be closest to a NOAEL (or might be considered a LOAEL). TERA pointed out that the data for the effects at this lowest dose were not shown in the report and that just one patient was tested at this dose. One reviewer questioned the appropriateness of this study given that these are sick patients being treated with perchlorate to bring them back to normal which is then labeled an adverse effect.

In defining the critical dose of the Stanbury and Wyngaarden (1952) study, the reviewers also discussed whether Graves' patients are more sensitive than normal humans to effects on the thyroid and thereby represent a sensitive subgroup allowing for a lower UF for intraspecies sensitivity. Dr. Fagin stated that he believes that the Graves' patients are more sensitive to perchlorate than healthy humans based on what is know about the mechanism of toxicity of perchlorate; however, there are not good comparative data to support this.

Uncertainty Factors: The reviewers were reluctant to discuss uncertainty factors because they felt that overall there were too many uncertainties with the choice and adequacy of the principal study and the available alternatives. However, several reviewers did suggest that if data were available to show conclusively that the thyroid effects are critical, then there is sufficient data on the mechanism to support the use of 3 or even 1 for the subchronic-to-chronic factor. The current database warranted use of a factor of 10, particularly because of the unknowns concerning other endpoints; but, the uncertainty in this area may be reduced by the conducting of a 90-day study and a developmental study (with neurological evaluation). The panel agreed that there were insufficient data at this time to warrant reducing the factor for sensitive subpopulations to less than 10.

TERA asked the reviewers what they would consider an appropriate interspecies uncertainty factor if the Caldwell data were used, given rat TSH levels are 100 times higher than humans, making rats a sensitive model. The reviewers indicated that they would want to see data to quantify this and that if a laboratory animal study were used, the human data should be used to adjust the uncertainty factors.

Confidence in the Value

The reviewers indicated that the poor nature of the existing database would lead to low confidence in any value developed from it.

Recommendations and Outstanding Issues

Overall, the panel concluded that the database for perchlorate was insufficient to support the development of an RfD. Several major questions are left unanswered by the existing data including the shape of the dose-response curve in humans, the effects of perchlorate after long-term exposure, and the possibility of effects in organs or systems other than the thyroid.

The panel made the following recommendations:

* A 90-day rat study with a developmental component and neurological evaluation is needed to answer a number of questions and reduce several uncertainties associated with the poor database. One reviewer commented that the Toxicology Division at Wright-Patterson Air Force Base had been planning at one time to conduct such a study and that their laboratory had a good reputation for this type of work.

* Expand discussion on effects of iodine deficiency, dietary goitrogens, and structurally similar ions for useful dose-response information.

* Further clarify the forms of perchlorate and provide information on dissociation constants or similar salts.

* Review data on the current pharmaceutical use of perchlorate and if the appropriate reevaluate data from some of the human studies, looking for additional information regarding the dose-response relationship of perchlorate in humans and data that can rule out concern over the aplastic anemia.

* Consult with Dr. Capen to determine the biological significance of hormone level changes observed in Caldwell et al. (1996). Use this information for estimating a benchmark dose from the Caldwell study.

* Find comparative data on rats and humans to quantify the rat's greater sensitivity to the iodide blocking effects of perchlorate.

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Attachment A Managing Potential Conflicts of Interest

TERA peer reviewers donate their time and talents to this effort. They are selected based upon their expertise and qualifications and are employed by many types of organizations. *TERA* strives to create a balance of expertise and affiliations; however, individual peer reviewers are representing their own expertise and views, not necessarily those of their employer.

TERA has requested that each peer reviewer identify potential conflicts of interest related to the review of a cadmium inhalation reference concentration (RfC), perchlorate oral reference dose (RfD) and the cancer assessment for dichloromethane. Each reviewer has signed a statement indicating that they do not have a conflict of interest concerning these chemicals; with the following exceptions noted below. *TERA* has discussed these potential conflicts with the individuals involved and a member of the *TERA* Board of Trustees. These were discussed at the March 6 and 7 meeting and the peer reviewers agreed to the following:

Robert Benson -- Dr. Benson works for the U.S. Environmental Protection Agency, Region VIII. He has developed the cadmium RfC and will be presenting it to the panel and therefore will not be a reviewer for that assessment. He does not have any conflicts with the other two chemicals and will participate fully in those reviews.

John Christopher - Dr. Christopher works for the California Environmental Protection Agency (Cal EPA). Cal EPA regulates various aspects of production, use, sale or disposal of virtually all chemicals; but he is not currently involved in any assignment or controversy regarding the toxicity of any of these three chemicals. However, Dr. Christopher lives near a Superfund site in Sacramento County which is owned by Aerojet, one of the PSG members, and where perchlorates have been found in groundwater.

Dr. Christopher had a passing involvement with this site in 1992, assessing dioxins while employed by a contractor of Aerojet. He is not currently involved with this site or perchlorates, however, his place of residence may raise a question of objectivity for some people. Dr. Christopher and *TERA* both think that his place of residence and/or previous employment would not have any influence on his objectivity as a scientist. In order to manage this appearance for a potential conflict, however, *TERA* recommended and the reviewers agreed that Dr. Christopher will participate in the discussions but not be polled for consensus. Dr. Christopher does not have any conflicts with the other two chemicals and will participate fully those reviews.

Gary Diamond -- Dr. Diamond works for Syracuse Research Corporation which has developed a cadmium oral RfD. Dr. Diamond believes and the reviewers agreed, that this will not influence his objectivity in assessing the proposed RfC. Dr. Diamond does not have any conflicts and will participate fully in all reviews.

Michael Dourson - Dr. Dourson works for Toxicology Excellence for Risk Assessment (*TERA*) which developed the perchlorate RfD for the Perchlorate Study Group. Dr. Dourson was personally involved in developing this RfD, and therefore, should not be a reviewer for that assessment, nor chair that portion of the meeting. He does not have conflicts with the other two chemicals and should participate fully in those reviews.

Marvin Friedman -- Dr. Friedman works for Cytec Industries. He does not have any conflicts with the three chemicals and should participate fully in all reviews.

Annie Jarabek -- Ms. Jarabek works for the U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. She was not involved in the development of the cadmium RfC being reviewed at this meeting in any way; including the writing of this RfC or the letting or managing of any contractual efforts for this RfC. She does not, therefore, have a conflict, real or apparent with the review of this file. The ORD office of the U.S. EPA that Ms. Jarabek works in, however, is developing a cadmium RfC for inclusion on the Agency's Integrated Risk Information System (IRIS). This RfC for IRIS is independent of that being reviewed at this meeting. Ms. Jarabek prefers not to be polled for consensus on this RfC to avoid the perception that this meetingÕs RfC is an Agency-wide consensus value and to preclude prejudice of her future involvement in development or review of the Agency RfC estimate. She does not have any conflicts with the other two chemicals and will participate fully in those reviews.

M.E. Meek -- Ms. Meek works for the Priority Pollutants Section of Health Canada. She is presenting the dichloromethane issues and therefore will not be a reviewer for that discussion. Ms. MeekÕs office assessed the toxicity of cadmium several years ago; however, she does not have a specific conflict with cadmium or perchlorate and will participate fully in those reviews.

Jon Reid -- Dr. Reid is on the faculty of the University of Cincinnati. He has no conflicts and will participate fully in all reviews.

Kenneth Poirier -- Dr. Poirier works for The Procter and Gamble Company. He has no conflicts and will participate fully in all reviews.

Ruthann Rudel -- Ms. Rudel works for the Silent Spring Institute. She has no conflicts and will participate fully in all reviews.

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